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Modified release of furosemide from Eudragits® and poly(ethylene oxide)-based matrices and dry-coated tablets

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Modified release of furosemide from tablet formulations is preferred by patients, because of physiological problems, acute diuresis being the most serious, compared to the forms designed for immediate release. With this in view, we aimed at achieving furosemide's longer gastric retention and waste minimization by preparing matrix and compression coated tablets incorporating different grades of Eudragit® and poly(ethylene oxide) (PEO), polyvinylpyrrolidone (PVP) and lactose monohydrate. Dissolution profiles of the new formulations were compared with that of the main stream drug Lasix®, 40 mg tablets. The results indicate that the use of Eudragit® in conjunction with either PVP or lactose monohydrate led to a slower release rate in the intestinal fluids compared to Lasix®. Moreover, furosemide release in the intestinal pH from matrix tablets and compression coated tablets was not noticeably different. Formulations incorporating PEO led to sustained release, in intestinal fluids, which depended on the molecular weight of PEO.

Keywords: matrix tablets, compression coated tablets, furosemide, Eudragit®, poly(ethylene oxide), polyvinylpyrrolidone

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Furosemide is widely used as a loop diuretic for the treatment of fluid retention (edema) of various origins, such as heart failure or kidney disease or high blood pressure. It is considered as the first line agent in people with edema caused by congestive heart failure and is the most commonly applied loop diuretic every year in the USA (1). Loop diuretics act at the ascending loop of Henle in the kidney and in contrast to thiazide diuretics, they are effective in patients with kidney diseases. More specifically, furosemide acts on the $Na^+/K^+/2Cl^-$ co-transporter in the thick ascending limb of the loop of Henle and inhibits re-absorption of sodium, chloride and potassium (2). Also, furosemide exhibits a weak carbonic anhydrase-inhibiting activity and increases urinary excretion of HCO_3^- and phosphate (3).

Furosemide bioavailability is variable (10–90 %) and can be improved when it is taken before meals. Furosemide is transported to the action site by binding to plasma proteins

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(4). Duration of its action is about 6 hours in case of oral administration and 2 hours when given intravenously. Furosemide is a week acid (pK_a = 3.9), poorly soluble in the upper gastrointestinal tract, but it has high permeability through the stomach and is categorized as Class IV in the biopharmaceutical classification system. Many studies have been performed concerning the solubility of furosemide. Its aqueous solubility is dependent on the pH of the medium, ranging from 0.18 mg mL^{-1}, at pH 2.3, to 13.36 mg mL^{-1}, at pH 10. Due to the pH-dependent solubility of furosemide, its absorption in humans is site-specific and takes place primarily in the upper parts of the small intestine (5). Researchers have already tried to increase its solubility by incorporating furosemide into cyclodextrins and by using some other novel drug delivery systems, like self microemulsifying drug delivery systems (SMEDDS), microparticles, Intelsite capsules, *etc.* (6–9). However, with its entrance into intestinal fluids, the drug releases rapidly from the currently used formulations, with a high peak of natriuretic and diuretic effect that causes displeasure to patients. This rapid release at the intestinal pH is due to the ionization of its carboxylic acid group. As a result, slower and more controllable intestinal release formulations are preferred because of a lower initial diuretic effect and a more extended duration of action.

In the last years, researchers have tried to develop a sustained release system of furosemide in order to improve the effectiveness of the drug. They have compared the efficiency of immediate release with modified release systems of furosemide for decreasing the fluid (edema) in the thoracic cavity (10). To this end, carbopol and sodium alginate were used and the results indicated that carbopol can extend the release of furosemide (11). Different viscosity grades of hydroxypropylmethyl cellulose (HPMC), microcrystalline cellulose and polyethylene glycol have also been used as excipients (12). Moreover, scientists have described the preparation and characterization of solid dispersions of furosemide with Eudragit® L100-55 (13), Eudragit® RL and RS, achieving controlled dissolution profiles with different carrier concentrations (14).

We have previously reported on the development of modified release formulations containing active substances of diverse chemical structures and physicochemical properties (15–21). Aiming at optimal delivery of furosemide, in order to provide more effective therapy, devoid of high peak natriuretic and diuretic adverse effects, its modified release profile from matrix and compression coated tablets is presented herein. Dry-coated tablets have all the advantages of compressed matrix tablets (*e.g.*, slotting, monogramming, speed of disintegration, *etc*.). Moreover, they are used to separate incompatible drug substances (one in the core and the other in the coat) and can provide a means of giving an enteric coating to core tablets; in contrast to compressed matrix tablets, dry-coated tablets can deliver the drug in a pulsatile fashion. More importantly, polymers in compression coating can serve as sustained release agents (22 and references cited therein). In this study, matrix and compression coated tablets, incorporating different grades of Eudragit® polymers and poly(ethylene oxide, PEO) (Polyox™), polyvinylpyrrolidone and lactose monohydrate were used. These excipients are commonly used for oral administration and can be easily formulated into matrix systems when it is required to modify the drug release rate from the solid dosage form. The different Eudragit® grades offer a great variety of physicochemical properties, depending on the release rate desired. We previously used PEO for the release of furosemide from hard gelatin capsules and the results showed that the low molecular weight polymers have a less extended sustained-release effect compared to the high molecular weight poly(ethylene oxide) (23).

EXPERIMENTAL

Materials

Furosemide was purchased from Sigma-Aldrich (Steinheim, Germany). The different grades of Eudragit® polymers L 100-55, L100, S100, RL100, RS were purchased from Rohm GmbH Pharma Polymers (Darmstadt, Germany). Poly(ethylene oxide) (M_r 0.9×10^6, 4×10^6, 5×10^6, 7×10^6), polyvinylpyrrolidone (PVP, average MW 10.000), and Sodium Lauryl Sulfate (SLS) were purchased from Sigma-Aldrich (Steinheim, Germany), lactose monohydrate was purchased from Merck, whereas magnesium stearate was obtained from Riedel-De Haen (Hannover, Germany). Lasix® 40 mg tablets are commercially available and were purchased from a local drug store. All chemicals were of reagent grade and were used in the study without further purification.

Methods

Preparation of Furosemide matrix and dry coated tablets

Each matrix tablet (formulations F1-F10 and F16-F28) comprised furosemide (60 mg) and combinations of the following excipients: different grades of Eudragit® polymer, PVP, lactose monohydrate, poly(ethylene oxide), SLS and magnesium stearate (as a lubricant). All the components (except for the lubricant) were blended in a mixing apparatus (Wab Turbula Type T2F) for 10 min (32 rpm). Magnesium stearate was then added to the mixture, which was blended for another 5 min. Total weight of each tablet was 200 mg, regardless of the composition, and tablets were produced using a 10 mm diameter die and a hydraulic press (Massen type, MP 150).

Formulations F11-F15 refer to dry coated tablets. The coating mixture comprised combinations of different grades of Eudragit® polymers with PVP and magnesium stearate as

Table I. Tablet composition of formulations F1-F15

Formulation (mg)		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
		Matrix tablets										Dry coated tablets				
Furosemide		60	60	60	60	60	60	60	60	60	60	60	60	60	60	60
Eudragit®	L100-55	70	–	–	–	–	70	–	–	–	–	70	–	–	–	–
	L100	–	70	–	–	–	–	70	–	–	–	–	70	–	–	–
	S100	–	–	70	–	–	–	–	70	–	–	–	–	70	–	–
	RL100	–	–	–	70	–	–	–	–	70	–	–	–	–	70	–
	RS100	–	–	–	–	70	–	–	–	–	70	–	–	–	–	70
Lactose		68	68	68	68	68	–	–	–	–	–	–	–	–	–	–
PVP 10,000		–	–	–	–	–	68	68	68	68	68	68	68	68	68	68
Mg Stearate		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Total		200	200	200	200	200	200	200	200	200	200	200	200	200	200	200

Table II. Tablet composition of formulations F16-F23

Formulation (mg)	F 16	F 17	F 18	F 19	F 20	F 21	F 22	F 23
Furosemide	60	60	60	60	60	60	60	60
Eudragit® L100	70	70	70	–	–	–	–	–
Lactose	40	34	28	–	–	–	–	–
PVP 10.000	28	34	40	–	–	–	–	–
Polyox™ 0.9×10^6	–	–	–	138	–	–	–	134
Polyox™ 4×10^6	–	–	–	–	138	–	–	–
Polyox™ 5×10^6	–	–	–	–	–	138	–	–
Polyox™ 7×10^6	–	–	–	–	–	–	138	–
SLS	–	–	–	–	–	–	–	4
Mg Stearate	2	2	2	2	2	2	2	2
Total	200	200	200	200	200	200	200	200

a lubricant. Components of the coating mixture (except for magnesium stearate) were blended in a mixing apparatus for 10 min and then magnesium stearate was added to the mixture, which was blended for another 5 min. The core of the tablets comprised Furosemide (60 mg) and magnesium stearate, and was formed using a 7.5 mm diameter die and hydraulic press (Massen type, MP 150). The core was placed in a 10 mm diameter die and the coating mixture (140 mg) was added. The final tablet was produced using a hydraulic press. Tables I and II illustrate the composition of tablets in each formulation.

Tablet uniformity tests

All tablets were evaluated for mass, hardness, thickness, drug content uniformity and friability.

Mass uniformity. – Twenty tablets or compression-coated tablets from each formulation were weighed individually using an electronic pan balance. The weight of each tablet was compared with the respective average weight of the tablets.

Crushing strength. – Crushing strength of tablets was determined using a hardness tester (Erweka, type TBH28) and the average value of three determinations was reported. Hardness strength is expressed in N (63.55–122.81 N).

Thickness. – Tablet thickness was measured with a Vernier caliper and the average of three determinations was calculated.

Friability. – Friability of the tablets was determined using a friabilator (Erweka, type TA3R). Percent friability is reported in terms of weight loss and has been calculated as percentage of the initial weight, according to Pharmacopeia specifications. Initial mass (W_0) of 33 tablets was weighed and put into a drum rotating at a rate of 25 rpm for 4 min. Tablets were then carefully dedusted with a soft brass deduster and reweighed (WR). Percent friability of the tablets was calculated using the following Eq. (*1*):

$$Friability = \frac{W_0 - W_R}{W_0} \times 100 \quad (1)$$

Drug content uniformity. – Three tablets from each batch were crushed in a glass mortar and dissolved singly in 100 mL sodium hydroxide in a stoppered conical flask, which was shaken in a mechanical shaker for 4 h. The samples were filtrated through a membrane filter and assayed for drug concentration using a Perkin-Elmer UV spectrophotometer (Norwalk, CT) at a wavelength of 274 nm. Calculation of drug content for each tablet was made using the standard curve. The percent of the label claim was used in the expression of the drug content for each tablet. Drug content not less than 90 and not more than 110 % of the active substance was considered acceptable (24).

Dissolution studies

The *in vitro* dissolution tests of the tablets were performed using a USP XXII dissolution apparatus II (Pharmatest Hainerp, Germany) (paddle method). Dissolution medium for the first 2 hours was 450 mL of a buffer solution pH 1.2 (HCl solution 0.2 mol L^{-1}) in order to simulate the stomach pH and then 450 mL of a buffer dissolution pH 9 (K_2HPO_4 solution, 0.14 mol L^{-1}) was added to obtain the required composition of the following phase, which simulated the enteric pH (pH 6.8, final volume 900 mL). The system was maintained at a controlled temperature of 37.0 ± 0.5 °C and the paddles were rotated at a rate of 50 rpm. Samples (5 mL) were taken at predetermined time intervals and passed through a 0.45 μm cellulose filter. At each time point, the volume was refilled with an equal volume of fresh medium. The concentration of furosemide released into the medium was measured using a Perkin-Elmer UV spectrophotometer (Norwalk, CT) at a wavelength of 274 nm and 234 nm when the dissolution medium was pH 1.2 and pH 6.8, respectively.

In order to compare the dissolution profiles of the formulation, graphs of the percent drug release *vs.* time were constructed and $t_{20\%}$, $t_{50\%}$, $t_{90\%}$ values were estimated. The $t_{20\%}$, $t_{50\%}$, $t_{90\%}$ values refer to the time when 20, 50 and 90 % of the active substance was released. The dissolution efficiency (*D.E.*) percent, a parameter used to estimate dissolution, was calculated according to the following Eq. (2) (25):

$$D.E. = \frac{\int_{t_1}^{t_2} y\,dt}{y_{100}\left(t_2 - t_1\right)} * 100 \quad (2)$$

where y is the percentage of dissolved product, *D.E.* is the area under the dissolution curve between time points t_1 and t_2, expressed as percentage of the curve at a maximum dissolution y_{100} over the same period.

Finally, the *in vitro* release data were fitted to the Korsmeyer-Peppas Eq. *3* (26, 27):

$$\frac{M_t}{M_\infty} = k * t^n \quad (3)$$

where is the percentage of the drug substance released, k is the release rate constant, t is the release time and n is the diffusion coefficient. This equation is valid for the first 60 % of fractional release. The n values represent either Fickian or non-Fickian release kinetics.

In particular, in the case of cylindrical tablets, $n > 0.45$ corresponds to Fickian diffusion release (Case I diffusion), $0.45 < n < 0.89$ to anomalous transport, $n = 0.89$ to zero order (Case II) and $n > 0.89$ to Super Case II release kinetics (28, 29).

RESULTS AND DISCUSSION

Tablet uniformity tests

Uniformity of mass. – Mass uniformity is used to evaluate the uniformity of formulations. Results in Table III indicate the value for weight deviation of < 1 %, which is signifi-

Table III. Results of uniformity tests: average mass expressed, crushing strength, thickness expressed, % friability and drug content

Formulation	Average weight (mg) Mean ± SD (n = 20)[1]	Hardness (N) Mean ± SD (n = 3)[1]	Thickness (mm) Mean ± DS (n = 3)[1]	Friability (%) (n = 33)[1]	Drug content uniformity (%) Mean ± SD (n = 3)[1]
Lasix®	161.6 ± 0.3	70.08 ± 1.23	2.3 ± 0.0	0.11	101.32 ± 0.78
F1	200.2 ± 0.8	120.69 ± 1.34	1.97 ± 0.6	0.12	100.78 ± 0.34
F2	200.4 ± 0.9	109.57 ± 0.56	1.8 ± 0.0	0.11	100.44 ± 0.62
F3	200.5 ± 0.7	72.77 ± 1.09	1.8 ± 0.0	0.69	102.56 ± 0.42
F4	200.3 ± 0.2	63.55 ± 0.39	1.8 ± 0.0	0.72	101.64 ± 0.31
F5	200.8 ± 0.7	72.28 ± 1.06	1.9 ± 0.0	0.78	100.37 ± 0.62
F6	200.1 ± 0.4	111.08 ± 2.21	1.9 ± 0.0	0.18	99.46 ± 0.84
F7	200.7 ± 0.4	88.06 ± 1.03	2.0 ± 0.0	0.44	101.12 ± 0.55
F8	200.9 ± 0.9	84.27 ± 1.50	2.0 ± 0.0	0.42	101.27 ± 0.61
F9	200.2 ± 0.1	65.87 ± 0.89	2.0 ± 0.0	0.72	100.36 ± 0.47
F10	200.3 ± 0.8	67.93 ± 0.83	2.0 ± 0.0	0.67	101.54 ± 0.63
F11	200.5 ± 0.8	103.56 ± 0.98	2.0 ± 0.0	0.14	101.3 ± 0.16
F12	200.2 ± 0.7	110.06 ± 0.98	2.0 ± 0.0	0.12	100.42 ± 0.18
F13	200.3 ± 0.2	98.00 ± 1.85	2.0 ± 0.0	0.18	100.61 ± 0.75
F14	200.7 ± 0.8	94.63 ± 0.45	1.9 ± 0.0	0.16	101.41 ± 0.71
F15	200.2 ± 0.8	96.82 ± 0.63	2.0 ± 0.0	0.19	101.24 ± 0.63
F16	200.8 ± 0.5	101.14 ± 0.99	2.0 ± 0.0	0.27	99.26 ± 0.13
F17	200.6 ± 0.7	102.61 ± 0.54	1.97 ± 0.6	0.24	101.29 ± 0.24
F18	200.2 ± 0.4	96.86 ± 0.50	2.0 ± 0.0	0.18	100.24 ± 0.18
F19	200.6 ± 0.5	122.81 ± 0.15	1.97 ± 0.6	0.17	102.37 ± 0.21
F20	200.2 ± 0.6	89.93 ± 0.26	1.97 ± 0.6	0.22	101.36 ± 0.44
F21	200.7 ± 0.8	119.28 ± 1.85	2.0 ± 0.0	0.18	100.32 ± 0.37
F22	200.3 ± 0.9	101.76 ± 1.13	1.97 ± 0.6	0.23	100.33 ± 0.58
F23	200.2 ± 0.1	67.60 ± 0.83	2.0 ± 0.0	0.78	101.1 ± 0.46

[1] n – the number of tested tablets

cantly less than ± 7.5 % from the official standard. As a result, all tablets passed the pharmacopeia requirements for weight variation (30).

Crushing strength. – Crushing strength test shows the ability of tablets to withstand pressure or stress during handling, packaging and transportation. The results (Table III) indicate that the maximum breaking force is within the acceptable crushing strength range (63.55–122.81 N) (31).

Thickness. – Thickness uniformity is used to evaluate the uniformity of formulations. Using the Vernier caliper method, employed in scientific laboratories and in manufacturing, the results shown in Table III indicate an acceptable value for thickness deviation of < 1 %.

Friability. – Results of tablet friability tests show that all the formulations had friability values ranging from 0.11 to 0.78 % (*m*/*m*) (Table III). According to USP, no formulation should have a friability value higher than 1.0 % (*m*/*m*); therefore, all formulations passed the test.

Drug content uniformity. – Results obtained from the assessment of the percent content of active ingredients in all furosemide formulations showed values within the USP monograph specifications (90–110 %) (Table III).

Table III illustrates the results of uniformity tests: average mass, crushing strength, thickness, percent friability and drug content.

Dissolution studies

To assess dissolution profiles, dissolution curves of the formulations were constructed and are depicted in Fig. 1.

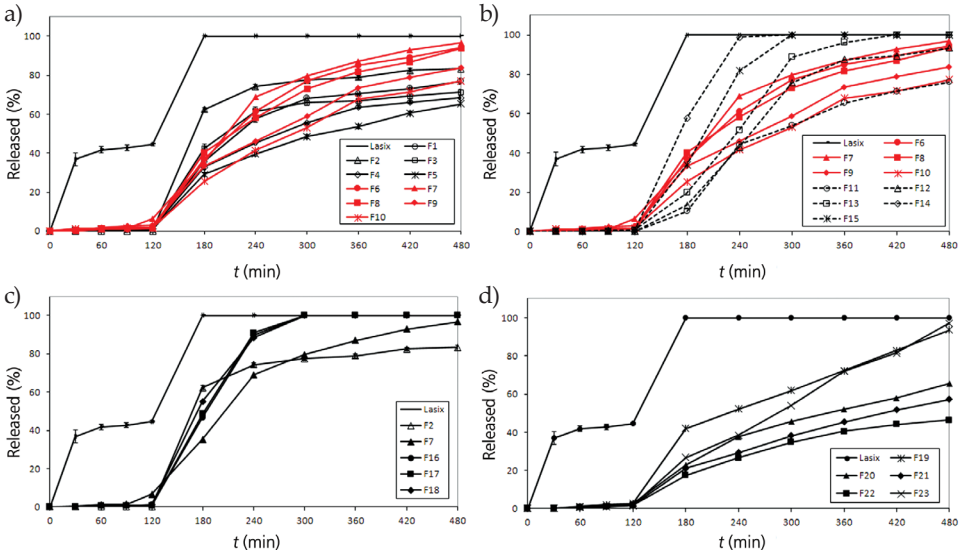

Fig. 1. Furosemide % release (mean values ± SD, $n = 3$) *vs.* time (min) from formulations: a) 1–10, b) 6–15, 2, 7, c) 16–18, d) 19–23 at pH 1.2 (0–2 h), at pH 6.8 (120–480 min).

Table IV illustrates the kinetic properties of drug release for Lasix® and the produced formulations. Terms $t_{20\%}$, $t_{50\%}$, and $t_{90\%}$ refer to the time when 20, 50 and 90 % of the dissolution is completed, respectively.

Fig. 1 illustrates the profile of furosemide release from the new formulations, which is compatible with both the gastroretentive and slower intestinal release requirements, with a well-defined absorption window. Precisely, at pH 6.8, the new formulations, which involve the pH dependant, water soluble polymers, Eudragit® L100-55, L100 and S100, permit facile water penetration into the tablet and consequently hydration of the formulation system leading to sustained drug dissolution. On the other hand, the use of water swellable polymers, Eudragit® RL and RS, which are not pH dependant, leads to lower release (Figs. 1a and 1b) (*D.E.* of F4 = 37.45 and F5 = 33.15 *vs*. F1 = 43.05, F2 = 54.69, F3 = 42.88). Analogous results were obtained by other researchers (32, 33).

Lactose is a water soluble excipient and has the potential to act as an agent that facilitates diffusion of the active substance from the hydrophilic polymeric matrix, since it leads to a more rapid relaxation of polymer chains. Therefore, lactose is considered one of the most suitable excipients used to accelerate the release of the active ingredient from controlled release systems from the hydrophilic polymer matrices (34). Substitution of lactose by PVP augmented the release of furosemide at pH 6.8 (Fig. 1a) (*D.E.* of F1 = 43.04 *vs*. F6 = 49.84 and F3 = 42.88 *vs*. F8 = 48.72). This PVP-owed furosemide percent release enhancement is in agreement with a recent literature report (35). A plausible explanation is that, at pH 1.2, protonation of the anilino-nitrogen of furosemide is preferable to -CO_2H protonation, even though the proximity of the amine and acid groups seems to allow a simultaneous interaction of the proton with both groups, thus stabilizing and delocalizing the charge more effectively (structures A and B) (Fig. 2) (36). With respect to PVP, it exists in the *gem*-diol form in the acidic medium (**III**, Fig. 3) (21), which does not facilitate furosemide dissolution, since H-bond formation between the OH of the diol and the anilino-nitrogen atom of furosemide is not feasible due to aryl-NH protonation (structure A).

Conversely, in neutral pH aqueous medium, H-bond formation is feasible between the oxygen atom of PVP (resonance structure **II**) and the aryl-NH hydrogen atom (structure B, Fig. 2), leading to the observed enhanced aqueous solubility of furosemide.

Fig. 1b illustrates the comparison of drug release from matrix and dry-coated tablets. It is observed that when the pH changes from acidic to neutral, at 120 min, the coating in

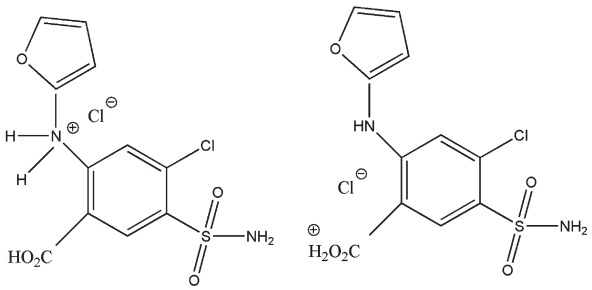

Fig. 2. a) Amine-protonated form of furosemide and b) the carboxylic acid-protonated form of furosemide.

Table IV. Kinetic properties of drug release for Lasix® and the produced formulations

Formulation	$t_{20\%}$	$t_{50\%}$	$t_{90\%}$	*D.E.*	n
Lasix®	15	125	170	79.36	0.13
F1	155	218	> 480	43.04	1.19
F2	125	162	> 480	54.69	3.29
F3	150	205	> 480	42.88	0.57
F4	158	265	> 480	37.45	0.78
F5	160	314	> 480	33.15	0.77
F6	152	212	420	49.84	1.08
F7	148	204	390	52.22	1.37
F8	148	213	448	48.72	0.83
F9	155	260	> 480	42.05	0.90
F10	167	284	> 480	37.61	0.98
F11	196	276	> 480	35.41	1.15
F12	193	250	421	44.45	1.18
F13	180	236	310	50.85	2.71
F14	140	172	225	63.39	–[a]
F15	155	200	262	58.22	–
F16	144	188	242	60.69	–
F17	144	184	239	61.35	–
F18	141	176	248	62.06	–
F19	147	228	456	45.17	0.81
F20	172	342	> 480	31.56	0.92
F21	176	404	> 480	26.98	0.98
F22	197	> 480	> 480	23.59	0.89
F23	162	282	455	40.43	1.32

D.E. – dissolution efficiency; *n* – diffusion coefficient estimated by the Korsmeyer-Peppas equation (Eq. 3).
[a] *n* values could not be calculated (release > 60 %).

formulations F14 and F15, consisting of Eudragit® RL-100, RS-100 and PVP, enhances the release of furosemide from the dry-coated tablets. Conversely, the coating in formulations F11, F12 and F13, consisting of Eudragit® L100-55, L-100 S-100 and PVP retards the release of furosemide from the dry-coated tablets (*D.E.* of F14 = 63.39, F15 = 58.22 *vs.* F11 = 35.41, F12 = 44.45, F13 = 50.85). Release of furosemide from matrix tablets containing the respective excipients (F6, F7 and F8) is generally higher. Release of the drug from the matrix tablets (F9 and F10) containing Eudragit® RL-100, RS-100 and PVP is lower than that from formulations F6-F8, (*D.E.* of F9 = 42.05, F10 = 37.61), F9 showing zero order kinetics (*n* = 0.90,

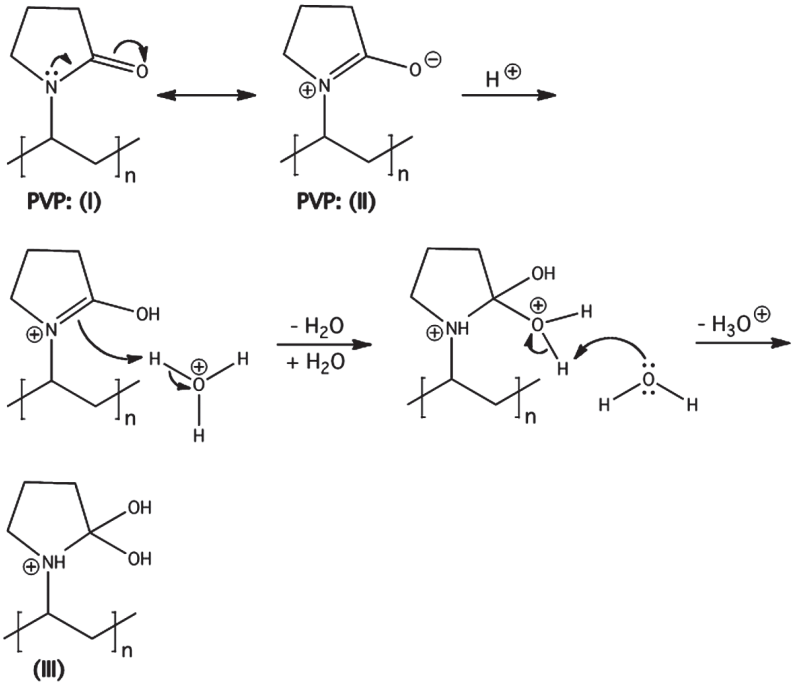

Fig. 3. PVP (**I**) conversion to *gem*-diol (**III**) (16).

Table IV). The release mechanism of furosemide from the dry-coated tablets in all cases corresponds to Super Case II release kinetics ($n > 0.89$) (Table IV).

When PVP and lactose were combined in different ratios into matrix systems, the drug dissolution increased in all cases, compared to the cases when these excipients were separately used (*D.E.* of F16 = 60.69, F17 = 61.35, F18 = 62.06, *vs.* F2 = 54.69, F7 = 52.22), (Fig. 1c, Table IV). This is probably due to the synergistic effect of PVP, which, as previously mentioned, exists at pH 6.8 in the ionic structure **II** form (Fig. 3), thus enhancing the overall ionic character of the lactose/PVP mixture.

Use of various molecular weight poly(ethylene oxide) results in different release rates, and this does not seem to be drastically affected by the presence or absence of the SLS surfactant (*D.E.* of F19 = 45.17, F23 = 40.43) (Fig. 1d, Table IV). It is well known that the lower the molecular weight, the greater is the drug release rate (37) (*D.E.* of F19 = 45.17, F20 = 31.56, F21 = 26.98, F22 = 23.59). Drug release from the low molecular weight poly(ethylene oxide) is strictly related to the polymer dissolution mechanism, while drug release from the high molecular weight poly(ethylene oxide) is principally related to material swelling and not to polymer dissolution (37). The drug release mechanism, when low molecular weight poly(ethylene oxide) (0.9×10^6) is used, corresponds to anomalous transport ($n = 0.81$). When higher molecular weight poly(ethylene oxide) (4 and 5×10^6) is used, the drug release kinetics corresponds to Super Case II ($n > 0.89$). When poly(ethylene oxide) molecular weight (7×10^6) is used, the release of furosemide becomes zero order ($n = 0.89$, Case II).

CONCLUSIONS

In general, the combinations of excipients used in this study, when compressed into matrix or dry-coated tablets, promoted modified release of furosemide in gastrointestinal-like environments. Release of furosemide from the systems examined in this study was found to be controllable and compatible with both the gastroretentive and slower intestinal release requirements, with a well-defined absorption window. The type of tablets affected both drug release and release mechanisms. These findings will be useful in the future *in vivo* studies.

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